IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Chen, et al.
Serial No. : 10/705,245
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Title : RISK ASSESSMENT FOR ADVERSE DRUG REACTIONS

Art Unit : 1634
Examiner : Stephen T. Kapushoc

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Commissioner for Patents
P.O. Box 1450
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DECLARATION OF YUAN-TSONG CHEN, MD, PH.D., UNDER 37 C.F.R. §1.132

I, Yuan-Tsong Chen, declare and state:

1. I am a co-inventor of the above-referenced application. I am a professor of pediatrics and genetics at Duke University Medical Center and also Director of the Institute of Biomedical Sciences at Academia Sinica, Taiwan, which is the assignee of this application.

2. I received a MD from National Taiwan University and a Ph.D. in human genetics from the Columbia University, New York, New York, in 1978. Prior to taking the directorship at Academia Sinica, I was Chief of Medical Genetics at Duke University Medical Center in Durham, North Carolina. My expertise in human genetics, particularly clinical molecular genetics, is evidenced by my *curriculum vitae*, a copy of which is attached herewith as Exhibit A. I was board certified in Clinical Genetics and Clinical Molecular Genetics by the American Board of Medical Genetics.

3. I am familiar with and understand the specification and current claims in this application. For example, claim 1 is directed to a method of assessing the risk of a human patient for developing an adverse drug reaction in response to a drug, comprising determining the presence of an HLA-B allele selected from the group consisting of HLA-B* 1502, HLA-B*5801 and HLA-B*4601, wherein the presence of the HLA-B allele is indicative of a

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risk for an adverse drug reaction selected from the group consisting of Stevens-Johnson syndrome and toxic epidermal necrolysis, and wherein the drug is carbamazepine or phenytoin.

4. I understand that the Office Action mailed May 17, 2006 is outstanding in this application. The Office Action rejects certain claims on the ground of non-enablement, alleging that the claims are not enabled commensurate with their scope. Specifically, with respect to the HLA-B*1502 allele, the Office Action alleges that the claims are enabled only for assessing the risk of a human Taiwanese patient for developing Stevens-Johnson Syndrome (SJS)/ toxic epidermal necrolysis (TEN) in response to carbamazepine (CBZ), wherein the presence of the HLA-B*1502 allele is indicative of an increased risk for SJS/TEN.

5. In my opinion, claim 1 is enabled commensurate with its entire scope. In the following paragraphs, I will discuss why the claimed method is enabled with respect to (1) all human patients, and (2) SJS or TEN in response to CBZ or phenytoin.

6. The Office Action states that the specification does not provide any analysis of non-human subjects, or any analysis of a non-Taiwanese population. The Office Action also states that it is unpredictable as to whether or not HLA-B*1502 would be indicative of a risk of an adverse drug reactions in another population, citing Hung et al.[1] and Lonjou et al.[2]

7. The strong association between HLA-B*1502 and CBZ- induced SJS/TEN is not limited to Taiwanese populations, since the subjects we analyzed in the examples of the present application were from Taiwan, Hong Kong, Mainland China, and the U.S. All of them were descendants of Han Chinese, and carry B*1502 alleles. In addition, one of the references cited by the Office Action, Lonjou et al., reports that four individuals with CBZ-induced SJS/TEN carried the HLA-B*1502 allele, and their places of birth were Vietnam, China, Cambodia, and Reunion Island, respectively. Another two research

[1] Hung et al., "HLA-B genotyping to detect carbamazepine-induced Stevens-Johnson syndrome: implications for personalizing medicine," Personalized Medicine (2005) 2(3):225-237.
[2] Lonjou et al., "A marker for Stevens-Johnson syndrome...: ethnicity matters", Pharmacogenomics J. (2006) 1-4.

groups from UK (Munir Pirmohamed) and Australia (Simon Mallal) also found Asian subjects developing CBZ-induced SJS/TEN carried B*1502 (personal communication). Thus, experimental data from Asian populations, beyond Taiwanese or Chinese, demonstrate a strong association between HLA-B*1502 and CBZ- induced SJS/TEN.

8. Furthermore, contrary to the assertion of the Office Action, Hung et al. support the notion that HLA-B*1502 is indicative of an increased risk of SJS/TEN in different populations. In Figure 2 of this reference, Hung et al. present a working model for the pathogenesis of CBZ-induced SJS/TEN. In this model, CBZ or its metabolite binds to a peptide, and the binding complex serves as a bridge between HLA-B*1502 of keratinocytes and T-cell receptors of cytotoxic T cells, causing HLA-B*1502-bearing keratinocytes to be recognized by cytotoxic T cells and inducing SJS/TEN. This model is consistent with the observation that HLA molecules are necessary for the activation of drug-specific T cells (see, *e.g.*, Hung et al., Page 232, right column, line 12, and reference 42 and 66 cited therein). Based on this model, any person having HLA-B*1502, regardless of the ethnic background, has a risk for CBZ-induced SJS/TEN.

9. Hung et al. further teach that HLA-B*1502 allele frequency positively correlate with the prevalence of CBZ-induced SJS/TEN in different populations (page 233 of Hung et al., left column, second paragraph). For example, at page 233, last paragraph of left column to first paragraph of right column, Hung et al. teach that the allele frequency of HLA-B*1502 is only 0-0.1% in Caucasians, which may explain the apparent lower incidence of CBZ-induced SJS in Caucasians. On the other hand, HLA-B*1502 is quite common in Malaysia, and CBZ is reported to be the major offending drug for SJS/TEN in that population.

10. The Office Action cites Hung et al. for teaching "alleles may be present in different frequencies in different populations, and that it is more likely to find a positive result when a study is conducted in a population with a high frequency of the allele (p.233, left col., lns. 8-13)." While this teaching indicates that it is less likely to find HLA-B*1502 in Caucasians, it does not mean that HLA-B*1502, once found in Caucasians, cannot be

used to predict the risk for developing SJS/TEN. Therefore, this teaching does not undermine the correlation between HLA-B*1502 and SJS/TEN.

11. The Office Action also alleges Hung et al. as teaching "as study results can vary between study populations, it remains to be seen to what extent the association between HLA-B*1502 and CBZ-induced SJS-TEN applies to other populations (p.233, right col., lns. 11-16)." In fact, the correct quote of the latter part should be "it remains to be seen to what extent the strong genetic association between HLA-B*1502 and CBZ-induced SJS/TEN applies to other populations" (emphasis added). As discussed above, the allele frequency of HLA-B*1502 varies among different populations. A person skilled in the art would recognize that if the allele frequency is low in a population, it may not be easy to obtain a statistically significant result using this population. In other words, if it is difficult to find sufficient Caucasians with HLA-B*1502 who have taken CBZ, one cannot perform a meaningful statistical study of the association between HLA-B*1502 and CBZ-induced SJS/TEN, let alone finding a strong genetic association. However, this technical difficulty does not reduce the correlation between HLA-B*1502 and CBZ-induced SJS/TEN.

12. The other reference, Lonjou et al., was cited as allegedly teaching "HLA-B*1502 is not a useful prediction marker of CBZ related SJS in the European population (p.3, left col., second paragraph)." This reference describes a preliminary study containing 12 European CBZ-induced SJS/TEN cases. Of the 12 patients, only 4 had an HLA-B*1502, and all 4 of them had an Asian ancestry. Lonjou et al. thus concluded that the HLA-B*1502 allele is not a universal marker and that ethnicity matters. This statement does not contradict the claimed invention. In the invention claimed in this application, the presence of HLA-B*1502 is used to indicate a higher risk for CBZ-induced SJS/TEN, rather than the other way around (predicting that CBZ-induced SJS/TEN patients should have the HLA-B*1502 allele). The fact that HLA-B*1502 is a risk factor for CBZ-induced SJS/TEN does not rule out the possibility that other risk factors may also exist. Similarly, the existence of other risk factors does not change the fact that the presence of HLA-B*1502 is indicative of increased risk for CBZ-induced SJS/TEN. The observation

of Lonjou et al. may reflect the low allele frequency of HLA-B*1502 in Europeans, but it does not render the claimed invention less predictable.

13. It should be noted that factors of low allele frequencies can be useful genetic markers as well. For example, the American College of Medical Genetics recommended 25 alleles of CFTR gene for routine diagnostic testing for cystic fibrosis (see, e.g., Tait et al.[3], Tables 6 and 7). Most of the 25 alleles are present in very low frequencies in Caucasians (see Table 7 of Tait et al.; the alleles not listed in Table 7 are even more rare), yet they are still recommended markers.

14. The claimed invention is applicable to at least SJS/TEN caused by CBZ or phenytoin. The Office Action agrees that the claims are enabled with respect to CBZ-induced SJS/TEN, but it asserts that the specification contains no measure of the statistical significance for drugs other than CBZ. I would like to draw the Examiner's attention to the following disclosure in Paragraph [0082] of this application:

> The allele was also found in 17 of 53 (32 %) SJS/TEN-patients who received other drugs (8 phenytoin, 2 allopurinol, 2 amoxicillin, 1 sulfasalazine, 1 ketoprofen, 1 Ibuprofen, and 2 unknown drugs). Particularly, eight of 17 patients (47.05%) who developed SJS/TEN after taking phenytoin also carry the HLA-B*1502 allele. On the other hand, the allele was only found in ... 0% (0/32) of the phenytoin-tolerant group... For B*1502 associated phenytoin-induced SJS/TEN, the odds ratio, sensitivity, specificity, positive predictive value, and negative predictive value were 58, 47%, 100%, 100%, and 65.35%, respectively. Accordingly, the presence of this HLA-B allele can be used in the identification of high-risk patients for drug-induced SJS/TEN, particularly carbamazepine- and phenytoin- induced SJS/TEN.

15. For the case of HLA-B*1502 and phenytoin-induced SJS/TEN, p value is 0.000053:

	Phenytoin-SJS/TEN (n=17)	Phenytoin-Tolerant (n=32)
Subjects with HLA-B*1502	8	0

[3] Tait et al., "Cystic fibrosis," Gene Clinics, posted March 26, 2001 at http://www.geneclinics.org/servlet/access?db=geneclinics&id=8888889&key=hTAmeSXYiaUo1&gry=INSERTGRY&fcn=y&fw=IRVN&filename=/profiles/cf/details.html (copy attached as Exhibit B)

Subjects without HLA-B*1502	9	32

P value = 0.000053 (P value was estimated by two-tailed Fisher's exact test; a P value of <0.05 was considered to indicate statistical significance.)

Odds ratio: 58.16 [95% Conf. Interval: 5.01~617.17] (Odds ratio was calculated with Haldane's modification, which adds 0.5 to all cells to accommodate possible zero counts. Haldane JB. The estimation and significance of the logarithm of a ratio of frequencies. Ann Hum Genet. (1956) 20(4):309-11.)

16. The Office Action also states that the specification teaches that 38 of the 42 carbamazepine-induced SJS/TEN patients also had the HLA-Cw*0801 allele, without a statistical analysis of the significance. The statistical analysis is provided below to address the Examiner's concern:

	Carbamazepine-SJS/TEN (n=42)	Carbamazepine-Tolerant (n=73)
Subjects with HLA-C*0801	38	12
Subjects without HLA-C*0801	4	61

P value = 1.8×10^{-15} (P value was estimated by two-tailed Fisher's exact test; a P value of <0.05 was considered to indicate statistical significance.)

Odds ratio: 48.29 [95% Conf. Interval: 14.94~154.04]

17. The Office Action further states that the specification does not provide any statistical analysis of the linkage between HLA-B*1502 and HLA-Cw*0801. It is well known in the art that HLA-B*1502 has a strong linkage disequilibrium with HLA-Cw*0801 (see, e.g., http://www.ncbi.nlm.nih.gov/projects/mhc/ihwg.fcgi). This public information, when coupled with our data that HLA-B*1502 is associated with CBZ or phenytoin-

induced SJS/TEN, would immediately lead a person skilled in the art to recognize that HLA-Cw*0801 is associated with the same medical conditions.

18. In summary, it is my opinion that the current claims are enabled to their full scope, including the use of HLA-B*1502 as an indicator of risk for CBZ or phenytoin-induced SJS/TEN in all human subjects who have HLA-B*1502. Furthermore, it should be noted that the CBZ and phenytoin in the claimed invention encompass their metabolites and analogs that have the same therapeutic applications as CBZ and phenytoin, respectively. The efficacy or dosage of each of these metabolites or analogs may be different from that of CBZ and phenytoin. However, to the extent the metabolite or analog can induce SJS or TEN, a method is enabled by the present application to assess the risk for such SJS/TEN, based on the presence of, e.g., HLA-B*1502.

19. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Respectfully submitted,

Date: Sept. 18, 2006

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